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EDITORIAL

Statins: pleiotropic, but less than previously thought

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This editorial refers to 'Effect of statins on ventricular tachyarrhythmia, cardiac arrest, and sudden cardiac death: a meta-analysis of published and unpublished evidence from randomized trials'†, by K. Rahimi *et al.*, on page 1571

Statins are undoubtedly the mainstay in the treatment of hyperlipidaemia. They are used in primary and secondary prevention of cardiovascular disease.[1,2] It is therefore not surprising that statins rank very high among the most successful drugs in the history of medicine. For example, atorvastatin has raked in around US$130 billion for Pfizer during its 14 years on the market, making it currently the world's bestselling drug.[3]

Recent studies show that statins possess powerful pleiotropic effects that are independent of their effects on lipids and lipoproteins.[4] The pleiotropic effects of statins are credited to several processes that result from the inhibition of hydroxy-methyl-glutaryl-CoA (HMGCoA) reductase. The main effect of the drugs is the inhibition of cholesterol and isoprenoid synthesis, which results ultimately in the up-regulation of endothelial nitric oxide synthase, an enzyme involved in vascular endothelial function. The inhibition of isoprenoid formation also leads to antioxidant effects. Additionally, inflammatory markers such as C-reactive protein and nuclear factor-κB have been shown to be reduced by statins, leading to the hypothesis that statins possess anti-inflammatory properties. Other proposed mechanisms for the pleiotropic effects of statins include immunomodulation, normalization of sympathetic outflow, plaque stabilization, decreased activation of the blood coagulation cascade, and inhibition of platelet aggregation.[4]

Pathophysiologically, mechanisms such as statin-induced plaque stabilization, changes to the transmembrane ion channel conduction, antioxidant and antiproliferative effects, and a decrease in the parasympathetic tone may potentially account for an antiarrhythmic effect of statin therapy which would at least be partially independent of the proven antiatherogenic effects of statin therapy.[5] In fact, the use of statins has been suggested to protect against various arrythmic disorders,[6,7] and a meta-analysis published in 2008 reported a significant reduction in the incidence or recurrence of atrial fibrillation in patients in sinus rhythm using statins.[8] However, in a more comprehensive collaborative meta-analysis of published and unpublished evidence from randomized controlled trials, the suggested beneficial effect of statins on atrial fibrillation was clearly not supported.[9]

What about the effect of statin treatment on ventricular arrhythmic complications? A very recent meta-analysis suggested that statins reduce the risk of ventricular tachyarrhythmia in patients with coronary artery disease or non-ischaemic cardiomyopathy by about one-third.[10] Rahimi *et al.* have now contradicted this finding.[11] In their meta-analysis of 29 trials with 113 568 participants comparing statin vs. a control, statin therapy did not significantly reduce the risk of ventricular tachyarrhythmia or cardiac arrest. Although the use of statins was associated with a significant 10% reduction of sudden cardiac death, a beneficial direct antiarrhythmic effect independent of the antiatherogenic effect of statin therapy seems very unlikely. Recently, a large autopsy series reported that coronary artery disease was responsible for sudden cardiac death in 37% of deaths in the group of those aged 21–30, and in up to 80% of deaths in the group of those aged 31–40.[12] When taking into account that statin therapy reduced other (non-sudden) cardiac deaths in included trials by ∼20%, an antiarrhythmic beneficial effect of statins independent of their antiatherogenic properties seems unlikely to account for the observed reduction in sudden cardiac death.

How can the discrepant findings of statin therapy on the occurrence of ventricular arrhythmias between these two recent meta-analyses be explained? A closer look at the two meta-analyses may help in resolving the apparent conflicting evidence. Both meta-analyses do not report substantial evidence of heterogeneity and both report a low likelihood of publication bias. However, the absence of heterogeneity and the low likelihood of publication bias exclude only two of many more potential pitfalls of meta-analyses leading to spurious conclusions. Of the nine identified prospective studies with a total of 150 953 individuals in the meta-analysis by Wanahita *et al.*,[10] only two were randomized controlled trials which together included <1000 individuals. All the other studies were observational, with one of these studies contributing ∼99%

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of all individuals included in the analysis. By using a more comprehensive literature search and by undertaking the effort to contact authors of large statin trials to contribute collected, but previously unpublished data on the incidence of ventricular arrhythmias, Rahimi *et al.*[11] identified 29 randomized controlled trials comparing statin with control with 113 568 individuals, >100 times more individuals than in the two randomized controlled trials identified by Wanahita *et al.*[10] In addition, Wanahita *et al.* did not conduct a formal critical appraisal of the quality of included studies and failed to report an assessment of the risk of bias in included studies as recommended by the PRISMA statement.[13] For these reasons, the results of the meta-analysis by Wanahita *et al.*[10] can only be regarded as hypothesis generating. Rahimi *et al.*,[11] by restricting their meta-analysis to randomized controlled trials and collecting all available published and unpublished data about the effects of statins on the risk of ventricular arrhythmias, now demonstrate that an antiarrhytmic effect of statins is highly unlikely.

Nowadays, clinicians quite often are faced with seemingly conflicting evidence from the medical literature. This may lead to uncertainty in clinical decision-making, especially for busy clinicians with time constraints not allowing them to read and analyse medical articles more in depth and focusing on abstracts only. In order to avoid misleading conclusions from abstracts of meta-analyses, all medical journals should adhere to the reporting guidelines as formulated in the PRISMA statement[13] that requires a structured abstract with an appraisal of the included studies as well as a description of the limitations of the meta-analysis.

The meta-analysis by Rahimi *et al.*[11] represents the currently best available evidence on the effect of statin therapy on ventricular arrhythmias and demonstrates clearly that statin therapy is highly unlikely to have a beneficial effect for the prevention of ventricular arrhythmias. Statins may still possess many pleiotropic effects, but independent antiarrhythmic effects do not seem to figure amongst them.

Conflict of interest: none declared.

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